A CONTRIBUTION TO THE PATHOGENESIS OF SOME EPILEPSIES. A PRELIMINARY CONTRIBUTION.[1]

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It is practically conceded, I believe, that there is more than one epilepsy. Clinically we recognize the classical forms of grand mal, petit mal, psychical equivalents, etc.; forms that dement rapidly, which are in marked contrast with those that do not. Pathologically a multiplicity of alterations have been described, all tending to show that different processes are active. Etiologically a similar variability of factors is observable.

Notwithstanding the desire to invoke the law of parsimony in our interpretations of epilepsy it remains that a mental survey of the work done upon the epileptic group reveals the fact that a single mode of interpretation for these disorders is unattainable, and that we are in the presence of a large group of very closely allied diseases of varying etiology, pathology, and clinical course, and that the grosser phenomena of the epileptic seizure have by their very prominence served to obscure the many minor points of variation, and to foster a narrow interpretation of this group of affections.

That the time has come for a more accurate study of different forms within the groups now so widely recognized, and an abandonment of the so firmly rooted conception that all epilepsies are alike and due to a single cause, is recognized by most students of these phenomena. Without burdening this communication with a host of citations from ancient and modern authors it will be readily conceded from this standpoint that many epilepsies are due to well-marked organic changes. Certainly the masterly studies of Alzheimer[2] on gliosis of the cortex and of the Ammon's horn and many others leave no ground for doubt in this direction.

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[1] Read at the thirty-third annual meeting of the American Neurological Association, May 7, 8 and 9, 1907.

[2] Monatschrift f. Neurologie u. Psychiatrie, Vol. IV.

We may naturally exclude at the outset the epilepsies due to tumors of the bones of the skull, meninges and brain, inclusive of echinococcus, porencephalic defects and cysts, traumatic lesions, scars, hypoplasias and microgyria of a hemisphere or a part of one, chronic leptomeningitis, encephalitis, and insular sclerotic atrophies. Other epilepsies have no such organic basis and an explanation must be sought on the basis of a yet unearthed disturbance of cellular metabolism. Munson's recent summary is illuminating in this direction. Further, other forms, and many of these offer fine problems in diagnosis, are interpretable on the hypothesis of a vaso-motor disorder with or without other factors. These three general factor groups, expressed in the broadest terms, do not by any means exhaust the field, but their statement is sufficient to emphasize the point of view here outlined.

Such a general point of view I believe will necessitate the closer analysis of the clinical findings and will afford valuable diagnostic, prognostic, and therapeutic outlooks. To illustrate in one direction alone. We all have been called upon to make a differential diagnosis between epilepsy and hysteria (both terms here being used as word diagnoses for symptom groups of different orders). The ablest of neurological students have confessed their inability to pin on a proper label in some of these patients, even after, at times, weeks of observation. Certainly such borderland conditions, if included within the epilepsy circle, are very different from the epileptic seizures in a diplegic idiot, and between these widely contrasting epilepsies there is a host of gradations. An epilepsy so closely resembling a hysteria or a psychasthenia has an entirely different pathological foundation, a widely variant prognostic outlook, and is in need of a quite dissimilar mode of therapeutic attack.

While not in any position to make a clinical differentiation of any group here, nevertheless it has been borne in upon me that there is a class of epilepsies which have a striking clinical resemblance, due as I believe to closely related etiological factors. There are the epilepsies following an acute poison of some nature; usually the toxin of an acute infectious disease. The epilepsies so prone to follow scarlet fever, measles, diphtheria, whooping cough, streptococcus infections, and influenza offer the most striking examples. It is unnecessary to quote the numerous studies that bear on these infectious diseases as factors in the etiology of from 5 to 10 per cent. of the cases subjected to the usual statistical inquiries.

While it is yet uncertain what are the affinities or perhaps lack of affinities of the poisons of these differing infectious diseases, and their relation to other poisons, it has been amply demonstrated by a number of workers in pathology that alterations in the character of the blood and changes in the walls of the blood vessels throughout the body are very characteristic, and it is not a far cry to apply the knowledge of such study on vascular alterations to such changes in the brain. Minute hemorrhages, capillary thrombi from agglutination, endothelial alterations are the precursors of the more extensive and permanent glia alterations, made necessary by the general phagocytic activity of these connective tissue elements. This introduces us to the subject of neuronophagia and its implications.

Having had under observation a striking example of poisoning by santonin in a young child with the production of a permanent epileptic state, I was tempted while in Munich last summer (1906) to make some experimental studies with this substance, in order to gain some information concerning its action on the cortex of lower animals. As this particular type of substance is well known to have an action on the motor cortex which is very striking, if not characteristic, it seemed an excellent opportunity for the carrying out of a histo-pathological research which might offer an interpretation for the histogenesis of some of the epilepsies that are met with clinically. I desire at this place to record my indebtedness to Dr. A. Alzheimer for his generous assistance while I was in the Psychiatric Clinic of Professor Kraepelin.

As I have already reported[3] the general clinical history of my patient I will give here only a brief summary of the striking facts.

The patient is a girl, the only child of healthy parents. She had always had fair general health, although somewhat nervous, and had always been much constipated.

In the evening of November 5, 1902, after passing a lumbricoid worm, the girl was given one santonin troche, U. S. P. (These troches are supposed to contain about one half grain santonin.) On the morning of November 6 she was given another troche of santonin and a tablespoonful of castor oil. The castor oil failed to act, and the girl had no movement on November 6.

At seven o'clock on the morning of the next day, November

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[3] Medical Record, March 31, 1906.

7, the mother noticed that the girl was unconscious and was in convulsions. How long the little girl had been so the mother did not know, as the patient made no outcry. She was then given a hot mustard bath and the family physician sent for. When he arrived at 7.30 A. M., November 7, the child was unconscious, and was having a spasm every fifteen minutes. She was given enemas, both superficial and deep. From 7 A. M., November 7, until 7 A. M., November 8, general convulsions occurred at intervals of from fifteen minutes to half an hour.

Beginning at 11.30 A. M. on November 7, chloroform inhalations were resorted to, to abort or relieve the spasms. These inhalations were kept up for twenty-four hours, or until the cessation of respiration during the spasms was so prolonged that it seemed inadvisable to employ it further. After the first twenty-four hours, it was necessary to resort to artificial respiration by the Sylvester method, during the spasms.

The patient recovered consciousness and spoke for the first time about 7 A. M., November 9—forty-eight hours after the onset of the attack.

The treatment of the patient during the stage of unconsciousness need not be here summarized as it is already available.

From November 9 on the restlessness and irritability were less and the interval between the convulsive attacks was lengthened. The patient soon began to show signs of exhaustion. When attacks came on the spasm of the respiratory muscles was so long that the patient became very much cyanosed. After the first day the patient could swallow nothing and was fed by the rectum.

At this time, and for three weeks following, the girl was blind, having scarcely any perception of light. No fundus changes could be detected. From November 9, the time of regaining consciousness, until November 25, a slight temperature elevation was noted, the girl was exceedingly restless, picking at the bedclothes and at her nose and ears, and keeping up a most exasperating cry most of the time.

The temperature had remained normal two weeks when December 10 there began to be a rise of one or two degrees in the evening, possibly due to a nephritis, which had been developing for some time. December 12, temperature 101° F.; December 13, temperature 102° F.; December 14, temperature 103° F.; December 15, 104° F.; December 16, 105° F.

December 16 she passed but eight ounces of urine. She was totally blind, restless; the skin was dry; the urine was loaded with albumin, and the feet were slightly swollen, eyes puffy.

The patient gradually recovered from the effects of the acute nephritis and by December 30, the temperature was normal and the albumin had disappeared from the urine. The girl's sight improved and returned to normal with the disappearance of the fever and the albumin. From this time on till January 20, 1903, there was a steady improvement in health and strength.

On or about the early part of February, 1903, the mother noticed that the child would suddenly fall down, or rather *sit* down, and as quickly get up and go on with her play, as if nothing had happened. This "sitting down" was a sudden bending of the thighs on the trunk, the knees remaining unbent. There was no cry, no pain, simply a sudden drop and up again, as though the muscles were weak and gave way. These fallings were more frequent during or after excitement. Usually they occurred about six to ten times a day. In March the girl began falling forward instead of sitting down, so that she frequently fell against the furniture and cut her face. In the latter part of April, 1903, the attacks ceased, but recommenced late in May or early in June of the same year, when she had from two to ten daily. Sometimes they lasted from half a minute to two (?) minutes. July 8, the attacks ceased for three days. July 11, the attacks recommenced more severely than ever.

On August 12 the physician was holding the child on his lap when she had a severe tonic spasm, very closely resembling an epileptic seizure. This attack continued for one minute, by the clock. The girl was in a sitting posture. Suddenly her head bent forward, her muscles were in a state of strong contraction. She cried out "Mamma, Mamma!" in a weak voice, and seemed to be in great pain. There was no suffusion of the face, no frothing at the mouth, and seemingly no unconsciousness. In a similar attack in the morning, she passed water, and while doing so she cried, "Oh, Mamma, I am peing!" She yawned several times immediately after the attack, and was evidently weak, but she showed no inclination to sleep.

While in my office at the time of the first consultation, the patient had two of the attacks, which have been characterized as simple muscular weakness. They were typically of this character. The girl, simply and without any loss of consciousness, seemed to sit down, or in one instance seemed more to slip, the floor being of polished wood. In no particular respect could it at this time have been recognized as a *petit mal* attack, notwithstanding the extreme variability of this type of epileptic seizure.

As for the distinct epileptic seizures, which ultimately developed, I have seen but one, and this was atypical. But the family physician has seen a number, and he has had a large experience with epilepsy in children. Thus there is little doubt in my own mind, at least, as to the correct diagnosis.

The further history is of interest. In a letter sent to me by Dr. Marshall, the family physician, he reports improvement:

"August, 1903, had fits, one, two or three times daily. Severe fits two or three times a week. September 12, 1903, began giving bromipin ʒ ii, three or four times daily. No appreciable effect. Continued until November 11. November 1 the mother reported that the 'falling spells' had ceased for a week (the dropping on the floor and getting up immediately, as described above), but that the 'real hard spells' were as numerous as ever. November 9 she reported that the child had had no fits during the day, but had had them in bed just before rising in the morning. November 11, 1903, began giving a bromide preparation. November 17, the child's legs were so weak that she staggered and could scarcely walk alone. Stopped the medicine one day, and then began giving it again, and have continued it to date, December 16, 1903. The girl has had no fits of any kind since November 9. The only other treatment beside the sedatives mentioned, has been the continued use, three times daily, of an intestinal antiseptic tablet."

On January 16, 1906, the family physician writes: "In reference to our patient, I would say that on looking over my book I find that the girl has had an attack which from the description, I presume to be epilepsy, about once in two months, since December, 1903. You have her history previous to that. Most of these attacks are very mild, and of only momentary duration. She had quite a severe fit on January 1, 1905. I was sent for, and the next day she showed the typical rash of measles, from which she recovered in about a week. In the fall I advised her mother to send her to a kindergarten. I am sure that the diversion and the getting away from her nagging mother has done her good. I expect her to recover fully some day. She has had from five to ten grains of brometone daily for varying periods, whenever she seemed nervous, and along about the first of the month, when an attack might be expected.

"My last report, just previous to going to press, February, 1908, is that the patient has not had a major attack for about a year, but that now and again attacks of dizziness occur, and the eyes turn to one side. On being addressed the patient pays no attention to what is being said, then in a few moments is all right. At these times while in class-room will execute automatic movements. On one occasion she marched out of school and came to herself on the stairs.

"Last attack was in November, 1907. On election morning, 1907, she had a nervous spasm, all of the muscles shaking. This was while asleep in bed. Intellectually she is on a par with others of her age."

Here was a striking case of poisoning by a comparatively well known substance which was followed by symptoms of marked cerebral irritation, by retinal edema, by edema of the kidneys, and by evidences of profound alterations in the blood vessels of these organs. This was followed by a condition of chronic epileptic convulsions due I believe to the alterations set up in the cortex.

The poisoning is not an isolated occurrence and the symptoms are classical, but the after-coming epilepsy is unique.

An examination as to the mode of action of santonin is of moment in this connection and as having a bearing on the subsequent animal experimentation a brief summary of our present knowledge concerning this substance may be of interest.

The pharmacology of santonin has attracted considerable attention, and for some time it was thought that the convulsive seizures to which its administration gave rise were of spinal origin, but of recent years the work of Turtschaninow,[4] Kramer,[5] Berkholz[6] and others has led to the belief that the epileptiform convulsions are due in the larger part at least to stimulation of the cortex—although it is highly probable that the medulla is involved as well. In Turtschaninow's experiments on dogs the sigmoid gyrus being removed epileptiform convulsions were not elicited, yet Luchsinger's[7] work, into which we cannot go at this time, might show that the entire spinal cord is finally excited to react in somewhat the same manner as with strychnine.

The symptoms as shown in the lower animals (rabbits) are very characteristic. After a small dose—0.1 to 1.0 gram of santonin to 1,500 grams of rabbit—in my experiments sodium santoninate was chosen as being soluble and as determined by previous observers, notably in Binz's experimental work,[8] showing the identical picture of poisoning—the animal commences to show in from ten to fifteen minutes marked increase in respiration and the pulse is quickened. The ears become redder and hotter, due to the increased blood supply and heightened respiration. Following the smaller dose this may be all that is observed. Following larger doses one observes in about a half hour after the injections the beginning of fine fibrillary contractions—the animals shiver and tremble but doses less than 0.8 gm. do not cause convulsions. In doses over one gram to 1,500 grams of animal convulsions commence to appear, and the development of the poisoning is more rapid.

Thus in a rabbit weighing 1,100 grams an injection of 1.5 grams of sodium santoninate was given at 9.20 A. M. At 9.30 breathing was very rapid; at 9.48 cramps began to appear, first in the muscles of the facial region. The nasal folds were elevated, the mouth was opened and closed with great rapidity; the rabbit jerked his neck back in clonic spasmodic movements. Respirations were 100. The spasms persisted a few moments only. The rabbit lay down quietly until 10 o'clock, when he suddenly arose, his head drew back, the limbs strongly extended; there were strong convulsive movements of the facial muscles at first, somewhat tonic in their character, and quickly followed by short, rapid clonic movements. These lasted only a few moments. The rabbit then ran about his cage, reacted to noises—had no loss of sight and apparently no variation of smell.

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[4] Arch. f. exp. Path. u. Pharm., 34, p. 208.

[5] Zeitschrift f. Heilkunde, XIV, p. 367.

[6] Dorpat Dissertation, 1893.

[7] Pflüger's Arch., 34, 1884, p. 293.

[8] Arch. f. exp. Path. u. Ph., 6, p. 300.

10.30, convulsion reappeared; in this attack the right leg was affected soon after the convulsions in the nose, eyelids and face; then generalized stiffness alternating with clonic convulsions occurred; opisthotonus developed, succeeded by rapid clonic spasms. This attack lasted about two minutes and was succeeded by a quiet period. 11, another attack, shorter in duration. 11.03, another, few muscle twitchings, first of mouth, the ears then drawn back, the teeth chattering, grinding, followed by strong tonic extension of all extremities, neck thrown back, opisthotonus, rising of animal on hind legs, clown-like tumbling over backward, the animal pitching over as a result of the clonic convulsive leg movements. The mouth continued to twitch throughout attack. Respiration 90. A few moments later a similar severe attack. Foam-like saliva exuding from mouth, increased secretion, chattering and grinding of teeth. From this time on the animal passed from one convulsion to another in a few moments with marked opisthotonus. 11.05, a similar attack, persisting 1½ minutes; 11.07 a slight attack; 11.09, severe attack with marked flexor contractions, signs of beginning weakness in fore-limbs; 11.20 rabbit unable to get up—twitchings and jerkings continue. Respiration 100, irregular; lay prostrate, exhausted from successive convulsive status. 11.27, opisthotonus strong, eyes closed; when opened noted sharp symptoms like jerks of eyeball. Pupils dilated, responsive to light. Rabbit lay on side, making ineffectual attempts to right itself. Strong contractions in muscles of neck, pawing the ground sideways with front- and hind-limbs. Clonic and tonic convulsions alternating, lightning-like twitches throughout entire body. 11.48, exitus, heart continued to beat two minutes after respiratory paralysis.

This is the picture in the fatal cases. Doses of 1.2 grams of sodium santoninate will cause several convulsions from which the rabbit recovers in from one to two hours, and next day is well and running about the cage, eating apparently in a normal manner. From the clinical evidence it would appear that the convulsions are of a mixed type, and it is certain that they are not all cortical.

Three rabbits were under observation. After obtaining a clear picture of the acute poisoning by gradually ascending doses, it was my object to study two things: first, the changes induced by acute poisoning, and, secondly, the alterations due to chronic poisoning. Rabbit 1, whose story has been given, served as material for the first purpose. It had been poisoned daily for a week in the effort to determine the lethal dose. Rabbits 2 and 3 were kept on smaller doses 0.2–0.3 grams for a week and the dose gradually raised to 1.0 gram of sodium santoninate daily. The giving of 1.0 gram caused for the first three weeks marked convulsive movements in Rabbit 2, weighing 1,400 grams, but not in Rabbit 3, of 1,525 grams; 1.2 grams was needed to influence the latter. A gradual toleration developed, but the two rabbits were kept on hypodermic doses varying from 1.2 to 1.5 grams of sodium santoninate daily for a period of about ten weeks. It was my intention to subject one rabbit to the action of santonin for a period of five months, but owing to technical difficulties one rabbit was lost and the other was utilized for a photographic analysis of the convulsive movements with the biograph apparatus. Excellent films were obtained.

A complete study of the lesions of the nervous system, confined for the most part to the study of the cortex was made of the case of acute poisoning. The two cases of chronic poisoning have not yet received complete study, only a few slides having been studied for the chronic changes. The further work in these must be left for a later period of quiet.

The lesions of acute santonin poisoning in the cortex are of interest, first as showing marked similarities to changes induced by other nerve poisons, and secondly as affording evidence that the mode of experimentation is valid and can lead to useful results if followed out more fully and completely than the time at my disposal would allow. It is essential that for the study of the changes of chronic poisoning, and through these the interpretation of the acute, that a period of over four months must be allowed.

Although complete detailed studied of the cytology of the rabbit's brain are still a desideratum, the work of F. Bailey forms an excellent standard of comparison for work of this nature.

The methods of examination employed were various. For the most part the Nissl and Cajal methods were used as routine procedures. Special fat stains were employed to ascertain the presence of fatty degeneration, and the Weigert glia method followed out for the study of these elements to determine their alterations in chronic poisoning.

I am unable to compare the results obtained with those of others, as no work known to me has been done on santonin since the advent of the finer cytological methods. Kobert remarks in the last edition of his monumental work on poisoning that such histological investigation of santonin poisoning is highly desirable. Bechholz,[9] working in Kobert's laboratory, confined his studies to dogs and investigated chiefly the mechanism of the movements. He compares the movements with those of epilepsy, in which he states he agrees with other authors before him. He maintains that the psychomotor cortex is the portion involved, but does not give any histological evidence.

Damme, in an interesting study largely directed to the investigation of the temperature variations, calls attention to the very widely dilated blood vessels of the periphery.

There is naturally a large literature bearing on the subject of yellow vision, but no clear understanding of the cause for this phenomenon is forthcoming.

The alterations, gross and cytological, following acute poisoning are very striking, although they have many parallels in other convulsion-producing poisons. Macroscopically an intense congestion of the meninges and of all of the cerebral vessels large and small is apparent. This is not due to the convulsive movements exclusively, for the dilatation of the blood vessels of the ears and the elevation in temperature of the ears were very striking in our experiments, and Damme has, as already cited, made a particular study of these phenomena. It is interesting to note that this marked peripheral dilatation is largely conservative, and is apparently a device to cool the blood as rapidly as possible, and thus avoid convulsive seizures, for among the many experiments made by Damme we find that if the animal is kept in an oven and this cooling is prevented there is a marked increase in the force and frequency of the convulsions. The redness and heat in the ears are pre-convulsive phenomena.

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[9] Experimentelle Studien über die Wirkung des Physostigmins, Santonin, Codeine, Cocaine, Strychnine und der Carbolsäure auf die psychomotorische Zone der Grosshirnrinde. Dorpat Dissertation, 1893.

Microscopically one finds the meninges and vessels tinged with blood, and minute capillary hemorrhages are common and widely diffused. The cortical vessels are more often involved. Whether increased pressure or vessel wall alteration or both are responsible, I have not yet been able to determine.

The changes in the ganglion cells, in brief, are those analogous to many acute poisons already made known by many investigators. They are not specific so far as I have been able to observe, yet the chromatolysis and nuclear alterations are not as marked as in many other poisonings.

Metachromatosis under Nissl treatment is a striking characteristic. The glia cells show no marked alterations. They take on a greenish tinge, however, and come out in strong contrast with the blue of the ganglion cell. In view of an interesting swelling that is observable in chronic poisoning the metachromatosis is worthy of recording.

The motor ganglion cells are uniformly altered. The large processes show the influences of being swollen; in fact, the entire ganglion cells show evidences by the vacuolation lines of having been swollen. The vacuolation is not a post-mortem alteration, nor do I believe an artefact. Its prominence in the main dendrites is of interest. Acute irregular swelling of the main dendrites is also observable. The Nissl bodies which are well ordered in the rabbit in the cells of the mid-psychomotor zone have lost their outlines, have become finely granular, or have suffered complete destruction. There is a marked chromatophilia of the cells. Remnants of intact Nissl bodies may be noted in places. Many cells are so widely changed that their death is undeniable. Marked changes in the nucleus beyond the marked chromophilia of the nucleolus were not observed.

The neuroglia was altered somewhat from normal neuroglia, yet in what direction it is difficult to say. The metachromatosis is peculiar and there is seen a marked tendency for a grouping or hugging of two or more glia cells about the base of the ganglion cells. What the significance of this is is uncertain.

One might go into considerable detail but the main facts brought out show for the acute poisoning marked alterations in the structure of the psychomotor zone. The ganglion cells are much altered, some are doomed to destruction, and there is a fairly constant reaction on the part of the connective tissue elements.

From the picture of the acute poisoning in animals it is a fair inference then to conclude that a similar acute process took place in the cortex of our patient, which was accompanied by some of the cell changes here noted. There is every reason to argue that the destruction of some ganglion cells took place, and we must turn to the chronic poisoning specimens to determine what were the subsequent developments in the cortex of the patient.

I have already intimated that I have been unable to finish my work on the chronic poisoning cases. This was due to the fact that the time chosen for the continuance of the poisoning was too short—ten weeks, it should have been at least four months—and that sufficient leisure has not been found to make the exhaustive search that such histological studies demand. The specimens of ten-week poisoning, however, do show enough to point the way in the direction of what takes place in the cortex after the acute process has passed.

From the observations to hand, following the death of the ganglion cells, a process of neuronophagia takes place. The precise character of this mechanism in chronic poisoning I have not yet been able to follow in many of its details, nor is there, in view of the work of René Sand on neuronophagia, any need of going over the evidence cited in this interesting monograph.[10]

Hajos,[11] in his excellent work on the cell changes in epilepsy, shows the effect of the same process, and the studies of Alzheimer, Franci, Weber, Orloff and others accentuate the value of the findings in this present study. Neuronophagia, or, as Marinesco prefers to call it, necrophagia, is a definite process in these experimental studies, and there is little doubt that it is the precursor to that gliosis which gradually replaces the site of the dead cells and which is such a characteristic picture in the brains of many epileptics.

In this preliminary communication all that I can hope to show is that following santonin poisoning there results a definite cellular alteration in the ganglionic areas of the psychomotor area, with death and destruction. This accounts for the profound functional disturbances resembling epileptiform convulsions. That as a result of chronic poisoning by the same substance a definite form of neuronophagia is demonstrated, which by inference from the many studies bearing on this subject, may be interpreted as a forerunner of a glial infiltration. Whether this latter will be found in my specimens I cannot yet say. Should such be the result, it would afford excellent evidence for a more definite understanding of the cellular mechanisms which lead to the gliosis of many chronic epilepsies. Should an opportunity offer, I hope to be able to complete the analysis of the specimens secured, and offer at greater length a number of interesting features of the research, which have not been included by reason of the preliminary character of this communication.

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[10] La Neuronophagie. Par René Sand, L'Académie Royale de Médecine de Belgique, Vol. XIX, 1906. Memoir Couronné.

[11] Hajos, Archiv f. Psychiatrie, Vol. 34, 1901.